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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/811,423	LUDWIG ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-7,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/14/07 has been entered.

Response to Amendments

Applicant's amendments filed 9/14/07 to claim 8 have been entered. No claims have been cancelled. Claims 13 and 14 have been added. Claims 1-14 remain pending in the current application, of which claims 8, 9, and 12-14 are being considered on their merits. Claims 1-7, 10, and 11 remain withdrawn from consideration at this time. Prior art references not included with this Office action can be found in a prior action.

For the record, claim 8 has not been amended to require that the cells in the culture express Oct4, as alleged by applicant at page 5, paragraph 2, of the Reply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is drawn to a composition comprising "a nutrient medium ... having an osmolarity in excess of 330 mOsMol," "wherein the osmolarity in the medium is optimized to support undifferentiated growth of the [human ES] cells." It is not clear how this "wherein" limitation further defines the claim, since the osmolarity is already particularly claimed at a quantitative level. It is not clear whether applicant is attempting to insert process-of-making steps into the claim, which would be improper, or rather simply to include an intended-use limitation in the claim. Clarification is required.

Because claims 9 and 12 depend from indefinite claim 8 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 13 is drawn to a composition comprising "a nutrient medium ... having an osmolarity in excess of 330 mOsMol," "wherein the quality index of the medium is optimal when osmolarity is in excess of 330mOsMol." Again, it is not clear how this "wherein" limitation further defines the claim, since the osmolarity is already particularly claimed at a quantitative level. Furthermore, it is not clear what criteria are used to define "optimal" in this "wherein" limitation, *e.g.* "optimal for supporting undifferentiated growth of the cells," *etc.* Clarification is required.

Claim 13 is drawn to a composition comprising, among other things, "undifferentiated human stem cells defined by expression of Oct4 marker in the medium," which is confusing. The wording of the claim implies that the cells express Oct4 marker into the medium. Clarification is required.

Because claim 14 depends from indefinite claim 13 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The rejection of record is withdrawn in light of the claim amendments and applicant's comments. However, after further consideration, the following new ground of rejection is imposed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 9, and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (2002, U.S. Patent Application Publication 2002/0076747) taken in view of Amit et al. (2000, *Developmental Biology* 227: 271-278; reference U).

Price teaches a composition comprising a culture plate; a nutrient medium (paragraph 128) therein; and mouse embryonic stem cells (ES-D3 cells) (Example 1, paragraphs 129-133).

Price does not exemplify a composition comprising human ES cells and does not exemplify a composition comprising nutrient medium of 330 or 350mOsm.

Price does suggest, however, that the osmolarity of the medium may be "as high as about 350mOsm" (paragraph 101) and that said medium is appropriate for culturing human ES cells (paragraph 102).

Amit teaches that human ES cells may be cultured in media originally optimized for mouse ES cells. Specifically, Amit teaches that human ES cells may be maintained in an undifferentiated state by growing them in KNOCKOUT DMEM supplemented with

KNOCKOUT serum replacement (both available from Invitrogen, Inc.; page 272, column 1, paragraph 3), and further supplemented with bFGF (Figure 1). The culture conditions of Amit maintain the expression of ES cell marker Tra-1-60 on the stem cells (page 273, column 2, paragraph 1).

The selection of osmolarity of the medium of Price would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Price et al. teach that the osmolarity may be up to about 350mOsm. The selection of the source of ES cells in the Example of Price would also have been a routine matter of optimization on the part of the skilled artisan, said artisan recognizing that Price teach that ES cells may be obtained from humans and cultured in the medium of their invention and that Amit teaches that human ES cells maintain an undifferentiated state (including the expression of at least one ES cell marker) in media optimized for mouse ES cells. A holding of obviousness over the cited claims is therefore clearly required.

The limitation "wherein the osmolarity in the medium is optimized to support undifferentiated growth of the cells" does not modify the scope of claim 8, which is drawn to a medium with a particular osmolarity. Whether or not Price acknowledged the alleged importance of osmolarity in the culturing of human ES cells, the fact remains that Price suggests media with the claimed osmolarity, and Amit provides specific motivation for culturing human ES cells in media originally optimized for mouse ES cells. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for

patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The limitation "wherein the quality index of the medium (MQI) is optimal when osmolarity is in excess of 330 mOsMol" does not modify the scope of claim 13, which is drawn to a composition in which the osmolarity is necessarily at least 330 mOsMol. Furthermore, as discussed above in the rejection under 35 U.S.C. § 112, second paragraph, it is not clear to what end the MQI is "optimal."

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that there are numerous material differences between mouse and human ES cells (Reply, section A starting at page 6). Applicant alleges that mouse ES cells require different culture conditions than human ES cells (Reply, section B starting at page 7). Applicant alleges that Price is silent as to medium quality (Reply, section C starting at page 8). Generally, applicant alleges that Price did not recognize the importance of osmolarity in culturing human ES cells (Reply, pages 6-10). These arguments have been fully considered, but they are not persuasive.

Applicant has supplied arguments that human ES cells are not equivalent in every way to mouse ES cells, and this point is not in dispute. However, the newly cited Amit reference teaches that these two types of cells are sufficiently similar that media optimized for one can be used to grow the other. Amit explicitly characterizes their DMEM formulation and serum replacement as "optimized ... for mouse ES cells," and

yet Amit teaches that human ES cells grown in the medium "continued active, undifferentiated proliferation throughout the culture period" (see the legend to Figure 1).

It is noted that Amit teaches that their media requires the presence of bFGF to maintain human ES cells in an undifferentiated state (see Figure 1A), but Price suggests that various growth factors may be added to their medium, depending on the needs of the cells and the species from which they are obtained (see paragraph 74). Taken together, the teachings of Price and Amit support the examiner's finding that at the time of the invention, modifying a mouse ES cell-optimized system such as that of Price to grow human ES cells would have constituted routine optimization. It is noted that the medium and serum replacement composition of Amit are same as those used by applicants in the working examples (see the as-filed specification at paragraphs 14-38).

Applicant alleges that since Price did not come to the same conclusions regarding optimal osmolarity and a measurement of media quality for growing human ES cells, the claimed compositions are not obvious. As discussed in the rejection above, the claims are drawn to compositions comprising particular components, in some cases in particular amounts. The reason for combining these components in these amounts cannot be the basis for patentability when said combining would otherwise be obvious.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart